Mechanisms to maintain the self-renewal and genetic stability of human embryonic stem cells

Grant Award Details

Mechanisms to maintain the self-renewal and genetic stability of human embryonic stem cells

Grant Type: Comprehensive Grant

Grant Number: RC1-00148

Investigator:

Name:	Yang Xu
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Cancer, Genetic Disorder

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $2,467,200

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: Mechanisms to maintain the self-renewal and genetic stability of human embryonic stem cells

Public Abstract:

Human embryonic stem cells (hESCs) are capable of unlimited self-renewal, a process to reproduce self, and retain the ability to differentiate into all cell types in the body. Therefore, hESCs hold great promise for human cell and tissue replacement therapy. Because DNA damage occurs during normal cellular proliferation and can cause DNA mutations leading to genetic instability, it is critical to elucidate the mechanisms that maintain genetic stability during self-renewal. This is the overall goal of this proposal. Based on our recent findings, I propose to investigate two major mechanisms that might be important to maintain genetic stability in hESCs. First, I propose to elucidate pathways that promote efficient DNA repair in hESCs. Second, based on our recent findings, I hypothesize that another primary mechanism to maintain genetic stability in self-renewing hESCs is to eliminate DNA-damaged hESCs by inducing their differentiation. Therefore, I propose to identify the pathways that regulate the self-renewing capability of hESCs in the presence and absence of DNA damage. In summary, the proposed research will contribute significantly to our understanding of the pathways important to maintain self-renewal and genetic stability in hESCs. This information will provide the foundation to improve the culturing condition of hESCs to promote efficient self-renewal with minimum genetic instability, a prerequisite for the development of hESCs into human therapeutics.

One major objective of the proposed research is to improve the genetic manipulation technologies in hESCs, including transgenic and gene targeting technologies. While mouse models are valuable tools to study the mechanisms of the pathogenesis in human diseases, many differences between mouse and human cells can lead to distinct phenotypes as well as the common phenomenon that certain therapeutic interventions work well in mouse models but poorly in humans. Therefore, it is of high priority to create disease-specific hESCs as powerful genetic tools to study the mechanism of the pathogenesis in human diseases. In addition, the unlimited supply of primary cells derived from the disease-specific hESCs will become valuable reagents for drug discovery. There are two ways to generate the disease-specific hESCs. One approach is through nuclear transfer that has been proven extremely difficult in human context and so far unsuccessful. The other is to employ the transgenic and gene targeting techniques to create disease-specific hESCs. Therefore, the proposed research will significantly improve our capability to generate disease-specific hESCs. After experimenting with various existing hESC lines, we found that only the non-federally-approved hESC lines developed recently at Harvard University is most suitable for genetic manipulation technologies. Since the research involving the HUES lines can not be supported by federal government, CIRM is in a unique position to support this proposed research.

Statement of Benefit to California:

Human embryonic stem cells (hESCs) are capable of unlimited self-renewal, a process to reproduce self, and retain the ability to differentiate into all cell types in the body. Therefore, hESCs hold great promise for human cell and tissue replacement therapy. The major goal of the human stem cell research supported by proposition 71 is to improve and even realize the therapeutic potential of hESCs. DNA damage occurs during normal cellular proliferation of hESCs and can cause genetic mutations that will be passaged to derivatives. Any cells with genetic mutations are not suitable for therapeutic purpose since they can cause cancers in the recipient. Therefore, to achieve the therapeutic potential of hESCs, it is critical to elucidate the mechanisms that prevent genetic mutations during the self-renewal of hESCs. This is the overall goal of this proposal. Successful completion of the proposed research will help to optimize the culturing conditions that promotes efficient self-renewal with minimum genetic instability.

One high-priority area of hESC research is to create disease-specific hESCs, which can be used as powerful genetic tools to study the mechanism of the pathogenesis in human diseases. In addition, the unlimited supply of primary cells derived from the disease-specific hESCs will become valuable reagents for drug discovery. There are two ways to generate the disease-specific hESCs. One approach is through nuclear transfer that has been proven extremely difficult in human context and so far unsuccessful. The other is to develop the transgenic and gene targeting techniques to create disease-specific hESCs. One major objective of my proposed research is to improve the genetic manipulation technologies in hESCs, including transgenic and gene targeting technologies. The successful completion of the proposed research will significantly improve our capability to generate disease-specific hESCs. In addition, the disease-specific hESCs (ATM-/- and p53-/- hESCs) generated in the course of the proposed studies are valuable tools to study the basis of neuronal degeneration in Ataxia-telangiectsia and development of human epithelial tumors as a result of p53-deficiency. Both of these phenotypes are not observed in mouse models.

In summary, the proposed research will benefit California citizens by contributing to the eventual realization of the therapeutic potential of hESCs.
